# Hemodynamic Support in Sepsis

Edoardo Antonucci, M.D., Bruno Garcia, M.D., M.Sc., Matthieu Legrand, M.D., Ph.D.

Sepsis is a dysregulated host response to infection responsible for life-threatening organ dysfunction.[1] Along with early antimicrobial administration and source control, correction of hemodynamic derangements is a crucial aspect of sepsis management. In this review, we will discuss the recent evidence in managing sepsis-induced hemodynamic alterations and how it can be integrated with previous knowledge for actionable interventions in adult patients. Fluid underresuscitation is associated with a risk of poor organ perfusion and excessive vasopressors use, while overresuscitation is associated with a risk of fluid overload and organ congestion (*i.e.*, pulmonary edema, abdominal compartment syndrome, acute kidney injury [AKI], liver injury). In this review, we will especially discuss the strategies for initial fluid resuscitation and vasopressors administration, the choice of fluid, and hemodynamic targets to guide resuscitation in adults.

## Initial Fluid Therapy and Vasopressors Strategy

The 2021 surviving sepsis campaign guidelines recommend 30 ml/kg crystalloids during the first 3 h of sepsis based on the median value observed in clinical trials.[2] This recommendation was empirical with a very low level of evidence,[2] and recent clinical trials have challenged this recommendation. While hemodynamic monitoring is most often limited or lacking during the very early phase of sepsis resuscitation, a more tailored approach to patient hemodynamic status using dynamic parameters or echocardiography is recommended to adjust fluid therapy to the hemodynamic profile during the subsequent stages[2] (fig. 1).

### Fluid Administration

The outcome benefit of large-volume fluid resuscitation (*e.g.*, greater than 30 ml · $kg^{-1}$ · $day^{-1}$) has been challenged over the past decade. Sepsis-induced organ injury can result from factors such as microvascular dysfunction, immune and autonomic dysfunction, apoptosis, mitochondrial damage, and coagulation disorders, which may potentially be exacerbated by fluid administration.[3] This risk underscores the need for a personalized intervention strategy to avoid excess fluid administration. Thirty percent of septic shock patients are not fluid responders in the early phase,[4] for whom fluids are not expected to provide benefit and are potentially harmful. In septic shock patients, a higher cumulative fluid balance at day 3 was independently associated with an increase in the risk of death.[5] In patients not undergoing active fluid resuscitation, the largest volume of fluids received in critically ill patients may often come from drug and maintenance fluid administration. Limiting these routine fluids should be a primary concern for clinicians.[6]

A restrictive fluid therapy approach was tested in the Conservative versus Liberal Approach to Fluid Therapy in Septic Shock (CLASSIC) and the Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) trials. In the CLASSIC trial, 1,554 patients with septic shock were randomized to a restrictive-fluid therapy, with fluid administration in cases of severe hypoperfusion, or in case of fluid losses, dehydration, or electrolyte deficiency, or to ensure a total of 1 l/day, *versus* standard fluid therapy[7] (table 1). Patients in the restrictive group received a median of 1,798 ml compared to 3,811 ml in the standard-fluid group. However, the 90-day mortality did not differ between groups.[7] The CLOVERS trial randomized 1,563 patients with sepsis-associated hypotension refractory to initial 1 to 3 l of intravenous fluids to a restrictive fluid strategy, which prioritized vasopressor use, or a liberal fluid strategy, which prioritized fluids administration.[14] The total median cumulative volumes of fluid administered, including the pre-enrollment fluids, were 3,300 ml (interquartile range, 2,550 to 4,350 ml) in the restrictive fluid group and 5,400 ml (interquartile range, 4,400 to 6,575 ml) in the liberal fluid group. Death before discharge did not differ between groups (14% *vs.* 14.9%).[14] Of note, a fluid-responsiveness assessment was not protocolized in these trials. Although such a restrictive strategy did not reduce mortality, it may have reduced the risk of harm from fluid administration in patients who are not fluid-responsive.

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Edoardo Antonucci, M.D.: Department of Anesthesia and Perioperative Care, Division of Critical Care Medicine, University of California, San Francisco, San Francisco, California; Department of Anesthesia and Critical Care Medicine, University of Milan, Milan, Italy.

Bruno Garcia, M.D., M.Sc.: Department of Anesthesia and Perioperative Care, Division of Critical Care Medicine, University of California, San Francisco, San Francisco, California; Department of Intensive Care, Centre Hospitalier Universitaire de Lille, Lille, France; Experimental Laboratory of Intensive Care, Université Libre de Bruxelles, Brussels, Belgium.

Matthieu Legrand, M.D., Ph.D.: Department of Anesthesia and Perioperative Care, Division of Critical Care Medicine, University of California, San Francisco, San Francisco, California; INI-CRCT (Investigation Network Initiative-Cardiovascular and Renal Clinical Trialists) Network, Nancy, France.

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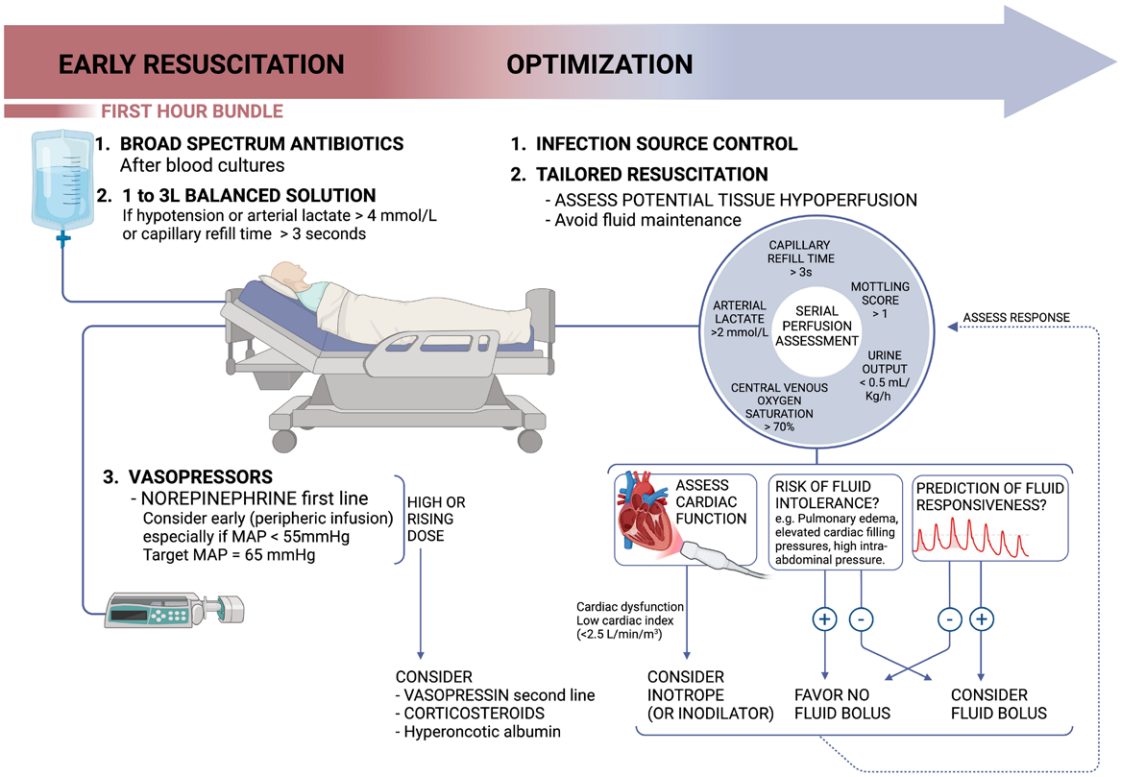


**Fig. 1.** Hemodynamic management of the septic patient: early resuscitation and optimization phases. The 4-h bundle includes the administration of broad-spectrum antimicrobial therapy after collecting blood cultures; fluid therapy to correct hypovolemia in hypotensive patients or those with signs of severe tissue hypoperfusion; and vasopressor administration, with norepinephrine as the first choice. Early vasopressors should be considered, with the possibility of peripheric vein infusion. During the early resuscitation phase, monitoring may be limited, and a mean arterial pressure of 65 mmHg is considered a reliable target. In patients with rising requirements of vasopressors dose, clinicians should consider a second-line vasopressor (*i.e.*, vasopressin), corticosteroids, and hyperoncotic albumin therapy. The optimization phase includes infection source control and a tailored resuscitation strategy based on serial reassessment. Signs of potential hypoperfusion such as hyperlactatemia, prolonged capillary refill time, skin mottling, abnormal central venous oxygen saturation, and contracted urine output should trigger a comprehensive hemodynamic evaluation and subsequent tailored interventions. The hemodynamic assessment should include bedside cardiac function estimation, determination of patients at risk of poor fluid tolerance (*e.g.*, signs of venous congestion, elevated cardiac filling pressure, pulmonary edema), and fluid responsiveness prediction, to drive inotropes, inodilators, and fluid therapy. Targeting better perfusion should serve as feedback to guide those interventions on individual patients' needs. MAP, mean arterial pressure. The figure was created with BioRender.com.

Dynamic measurement of preload responsiveness (using heart-lung interactions such stroke volume variation, pulse pressure variation, or response to a passive leg raise or a fluid bolus) can assess the effectiveness of fluid boluses in increasing stroke volume[26–28] (table 2). Although many studies have assessed their predictive value for short-term fluid responsiveness, their impact on outcomes remains uncertain,[29] and data on the impact of outcome of using dynamic measurement of preload responsiveness are very limited.

Dynamic measurement of preload responsiveness was tested against usual care in 124 patients with sepsis-associated hypotension and found a statistically significant reduced fluid balance at 72 h (–1.37 l), less need for renal replacement therapy (5.1% *vs.* 17.5%), and less need for mechanical ventilation (17.7% *vs.* 34.1%).[8] A meta-analysis of randomized controlled trials showed no difference in mortality among septic shock patients treated with fluid responsiveness-guided resuscitation *versus* those with standard care,[30] but the limited number of patients enrolled (n = 365) and heterogeneity of patients enrolled are important limits.

Importantly, fluid responsiveness is time dependent. In a prospective multicenter study of 143 septic shock patients, 49% initially responded with a greater than 15% increase in stroke volume after 500 ml crystalloid infusion longer than 10 min but became nonresponders within 20 min.[31] Moreover, the macrohemodynamic improvements from fluid boluses may not be sustained. In a prospective study of 500 observations, the significant increase in mean arterial pressure (MAP; +4 mmHg) and decrease in heart rate (HR;

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**Table 1.** Major Randomized Clinical Trials

| Publication | Population and Setting | Main Inclusion Criteria | Comparison | Primary Outcome | Main Results | Conclusions |
|---|---|---|---|---|---|---|
| Tailored fluid administration | | | | | | |
| CLASSIC; Meyhoff, 2022[7] | 1,554 patients with septic shock in 31 ICUs across Europe. | Adult patients in the ICU with septic shock onset within 12 h before screening, defined as suspected or confirmed infection, a plasma lactate ≥2 mM, infusion of a vasopressor or inotropic agent, and receipt of at least 1 l IV fluids in the 24 h before screening. | Restrictive IV fluid therapy *vs.* standard IV fluid therapy. | Death within 90 days after randomization. | 323 of 764 patients (42.3%) in the restrictive-fluid group and 329 of 781 patients (42.1%) in the standard-fluid group had died at 90 days (adjusted absolute difference, 0.1%; 95% CI, –4.7 to 4.9; $P = 0.96$).<br>The restrictive-fluid group received a median of 1,798 (interquartile range, 500 to 4,366) ml of IV fluid; the standard-fluid group received a median of 3,811 (interquartile range, 1,861 to 6,762) ml.<br>No significant difference in secondary outcomes (serious adverse events in the ICU, AKI, days alive without life support, and days alive and out of the hospital at 90 days). | In adult ICU patients experiencing septic shock, the implementation of IV fluid restriction did not lead to a reduction in 90-day mortality compared to standard IV fluid therapy. |
| Douglas, 2020[8] | 124 patients with sepsis-associated hypotension in the emergency department of 13 hospitals in the United States and United Kingdom. | Adult patients presenting to the emergency department with sepsis or septic shock (defined as ≥ 2 systemic inflammatory response syndrome criteria and a suspected or documented infection) and anticipated ICU admission; MAP ≤ 65 mmHg after receiving ≥ 1 l and < 3 l of fluid; enrollment within 24 h of hospital arrival. | Resuscitation guided by a dynamic assessment of fluid responsiveness (passive leg raise) *vs.* usual care. | Difference in positive fluid balance at 72 h or ICU discharge. | Patients receiving resuscitation guided by dynamic fluid responsiveness assessment had a reduced fluid balance at 72 h (–1.37 l; $P = 0.021$), less need for renal replacement therapy (5.1% *vs.* 17.5%; $P = 0.04$), and less need for mechanical ventilation (17.7% *vs.* 34.1%; $P = 0.04$). | Utilizing physiologically informed resuscitation is a safe approach to managing septic shock. This method was shown to reduce net fluid balance and lower the risk of renal and respiratory failure. Dynamic assessments for fluid administration may enhance outcomes in sepsis. |
| Which fluid? | | | | | | |
| SMART; Semler, 2018[9] | 15,802 critically ill patients in 5 ICUs at an academic center in the United States. | Adult patients admitted to a participating ICU. | Balanced crystalloids (lactated Ringer's solution or Plasmalyte) *vs.* 0.9% saline solution. | Major adverse kidney event at 30 days (composite of death, new renal replacement therapy, or persistent renal dysfunction, whichever occurred first). | 1,139 of 7,942 (14.3%) in the balanced crystalloids group and 1,211 of 7,860 patients (15.4%) in the saline group had major adverse kidney events at 30 days (odds ratio, 0.90; 95% CI, 0.82 to 0.99; $P = 0.04$)<br>In a subgroup of 1,641 patients with sepsis, the 30-day in-hospital mortality was 25.2% in the balanced crystalloids group *vs.* 29.4% in the saline group (adjusted odds ratio, 0.80; 95% CI, 0.67 to 0.97; $P = 0.02$). | In critically ill adults, utilizing IV balanced crystalloids led to a reduced incidence of major adverse kidney events compared to the use of saline.<br>The difference in outcomes in favor of balanced crystalloids and saline seemed more pronounced among patients with sepsis. |
| SAFE; Finfer, 2004[10] | 6,997 critically ill patients in ICU in 16 academic hospitals in Australia and New Zealand. | Adult patients admitted to the ICU, deemed by the treating clinician to necessitate fluid administration to maintain or increase intravascular volume, supported by meeting at least one objective criterion. | 4% albumin *vs.* 0.9% saline solution. | Death from any cause within 28 days after randomization. | 726 of 3,497 (20.8%) in the albumin group and 729 of 3,500 (20.8%) in the saline group had died at 28 days (relative risk, 0.99; 95% CI, 0.91 to 1.09; $P = 0.87$).<br>In a subgroup of 1,218 patients with severe sepsis, 28-day mortality was 30.7% in the albumin group *vs.* 35.3% in the saline group (relative risk, 0.87; 95% CI, 0.74 to 1.02). | In critically ill patients, employing either 4% albumin or 0.9% saline for fluid resuscitation yielded comparable outcomes at 28 days. This lack of significant difference in outcomes persisted within the subpopulation of septic patients. |

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**Table 1.** (Continued)

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| ALBIOS; Caironi, 2014[11] | 1,818 patients with severe sepsis in 100 ICUs in Italy | Adult patients who met the following criteria, within the previous 24 h at any time during their ICU stay: (1) proved or suspected infection; (2) two or more of the following (core temperature ≥ 38°C or ≤ 36°C, HR ≥ 90 beats/min, respiratory rate ≥ 20 breaths/min or $Paco_2$ ≤ 32 mmHg or use of mechanical ventilation for an acute process, leukocyte count ≥ 12,000/ml or ≤ 4,000/ml or immature neutrophils >10%); (3) at least a severe and acute sepsis-related organ dysfunction, as measured by the modified SOFA score. | 20% albumin and crystalloid solution *vs.* crystalloid solution alone. | Death from any cause within 28 days after randomization. | 285 of 895 patients (31.8%) in the albumin group and 288 of 900 (32.0%) in the crystalloid group had died at 28 days (relative risk, 1.00; 95% CI, 0.87 to 1.14; $P = 0.94$).<br>The albumin group had a higher MAP ($P = 0.03$) and lower net fluid balance ($P < 0.001$) during the first 7 days of study.<br>Patients with septic shock who received albumin had a lower risk of 90-days mortality (relative risk, 0.87; 95% CI, 0.77 to 0.99; relative risk without septic shock, 1.13; 95% CI, 0.92 to 1.39). | For patients with severe sepsis admitted to the ICU, the addition of albumin replacement to crystalloids, as opposed to crystalloids alone, did not improve the 28-day survival rate. |
| SWIPE; Mårtensson, 2018[12] | 321 patients requiring fluid resuscitation in 3 ICUs in Australia and the United Kingdom. | Adult patients hemodynamically unstable (one or more of the following physiologic states: [1] systolic blood pressure < 90 mmHg; [2] MAP < 65 mmHg; [3] increasing need for vasopressor; [4] pulse pressure variation 12%; [5] stroke volume variation 12%; [6] Cardiac Index < 2.2 l/min/$m^2$, or HR > 100; [7] urinary output < 20 ml/h; [8] either rising lactate levels or lactate levels > 2 mM or capillary refill time > 3 s or central venous pressure < 8 mmHg), requiring an IV fluid bolus as determined by independent treating clinicians. | 20% albumin *vs.* 4% (Australia) or 5% (United Kingdom) albumin. | Cumulative volume of resuscitation fluid in the first 48 h after randomization. | The cumulative volume of resuscitation fluid at 48 h was lower in the 20% albumin group than in the 4 to 5% albumin group (median difference, −600 ml; 95% CI, −800 to −400).<br>The proportion of patients who required renal replacement therapy was 3.3% in the 20% albumin group and 4.2% in the 4 to 5% albumin group ($P = 0.67$).<br>The proportion discharged alive from the ICU was 97.4% in the 20% albumin group and 91.1% in the 4 to 5% albumin group ($P = 0.02$). | Resuscitation with 20% albumin reduced fluid requirements and showed no evidence of harm when compared to 4 to 5% albumin. |
| Early vasopressors administration | | | | | | |
| CENSER; Permpikul, 2019[13] | 310 patients with hypotension and sepsis in the emergency department of a single center in Thailand. | Adult patients admitted at the emergency department with a MAP < 65 mmHg, suspected infection, and meeting the diagnostic criteria for sepsis as per the Surviving Sepsis Campaign, for <1 h. | Early norepinephrine administration *vs.* placebo. | Shock control rate by 6 h after diagnosis, defined as achievement of MAP > 65 mmHg, with urine output > 0.5 ml/kg/h for 2 h, or decreased serum lactate > 10% from baseline. | 118 of 155 patients (76.1%) in the early norepinephrine group and in 75 of 155 (48.4%) in the control group achieved shock control by 6 h ($P < 0.001$).<br>The early norepinephrine group exhibited lower occurrences of cardiogenic pulmonary edema (22 of 155, 14.4% *vs.* 43 of 155, 27.7%; $P = 0.004$) and new-onset arrhythmia (17 of 155, 11% *vs.* 31 of 155, 20%; $P = 0.03$). | The early administration of norepinephrine in patients with hypotension and sepsis resulted in an improvement of shock control within 6 h. |

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**Table 1.** (Continued)

| Publication | Population and Setting | Main Inclusion Criteria | Comparison | Primary Outcome | Main Results | Conclusions |
|---|---|---|---|---|---|---|
| CLOVERS; Shapiro, 2023[14] | 1,563 patients with refractory sepsis-induced hypotension in 60 centers in the United States. | Adult patients with suspected or confirmed infection (defined as the administration of antibiotic drugs) and within 4 h of evidence of sepsis-induced hypotension (systolic blood pressure < 100 mmHg after the administration of 1,000 to 3,000 ml IV fluid). | Restrictive fluid strategy *vs.* liberal fluid strategy for 24 h. | Death from any cause before discharge home by day 90. | 109 patients (14%) of the restrictive group and 116 patients (14.9%) in the liberal group had died in the hospital (estimated difference, –0.9%; 95% CI, –4.4 to 2.6; $P = 0.61$).<br>Vasopressors use was more frequent (21.7%; 95% CI, 16.9 to 26.6) and started earlier (–1.4 h; 95% CI, –2.0 to – 0.8) and patients had received less fluids in the restrictive group (difference of medians, –2,134 ml; 95% CI, –2,318 to –1,949). | In patients with sepsis-induced hypotension, a restrictive fluid strategy did not lead to significantly different mortality before discharge home by day 90 compared to a liberal fluid strategy. |
| Which vasopressor? | | | | | | |
| SOAP II; De Backer, 2010[15] | 1,679 patients with shock in 8 centers in Belgium, Austria, and Spain | Adult patients with shock, defined as MAP < 70 mmHg or systolic blood pressure < 100 mmHg despite fluids had been administered (≥ 1,000 ml crystalloids or ≥ 500 ml colloids), unless there was an elevation in cardiac filling pressures, and if there were signs of tissue hypoperfusion (*e.g.*, altered mental state, mottled skin, urine output < 0.5 ml · kg$^{-1}$ · h$^{-1}$, or serum lactate level > 2 mM). | Dopamine *vs.* norepinephrine. | Death from any cause within 28 days after randomization. | 52.5% in the dopamine group and 48.5% in the norepinephrine group had died at 28 days (odds ratio, 1.17; 95% CI, 0.97 to 1.42; $P = 0.10$).<br>207 (24.1%) arrhythmic events in the dopamine group *vs.* 102 (12.4%) events in the norepinephrine group ($P < 0.001$).<br>In the subgroup of patients with septic shock (1,044), dopamine was not significantly associated with an increased rate of death at 28 days ($P = 0.19$ in Kaplan–Meier analyses). | While there was no significant difference in the mortality rate between patients with shock receiving dopamine as first-line vasopressor agent and those receiving norepinephrine, dopamine use was linked to a higher incidence of adverse events. |
| VANISH; Gordon, 2016[16] | 409 patients with septic shock in 18 ICUs in United Kingdom. | Adult patients with sepsis (meeting two of four systemic inflammatory response criteria due to known or suspected infection) and necessitating vasopressors despite adequate IV fluid resuscitation, as determined through clinical examination, central venous pressure, oxygen saturation, or other physiologic parameters with the use of repeated fluid challenges. | Vasopressin plus hydrocortisone *vs.* vasopressin plus placebo *vs.* norepinephrine plus hydrocortisone *vs.* norepinephrine plus placebo. | Kidney failure–free days: (1) proportion of survivors who never developed kidney failure; (2) median number of days alive and free of kidney failure for the other patients who did not survive, who experienced kidney failure, or both at any time. | The number of survivors who never developed kidney failure was 94 of 165 patients (57.0%) in the vasopressin group and 93 of 157 patients (59.2%) in the norepinephrine group (difference, –2.3%; 95% CI, –13.0% to 8.5%).<br>The median number of kidney failure–free days for patients who did not survive, who experienced kidney failure, or both was 9 days (interquartile range, 1 to –24) in the vasopressin group and 13 days (interquartile range, 1 to –25) in the norepinephrine group (difference, –4 days; 95% CI, –11 to 5). | In adults with septic shock, the early administration of vasopressin, as compared to norepinephrine, did not enhance the number of kidney failure–free days. While these results do not justify substituting vasopressin for norepinephrine as the initial treatment in this context, a potential clinically significant benefit for vasopressin cannot be excluded. |
| ATHOS-3; Khanna, 2017[17] | 344 patients with vasodilatory shock in 75 ICUs across nine countries in North America, Europe, and Australasia. | Adult patients with vasodilatory shock (cardiac index > 2.3 l · min$^{-1}$ · m$^3$ or central venous oxygen saturation > 70% coupled with central venous pressure > 8 mmHg, with a MAP between 55 and 70 mmHg) despite IV volume resuscitation with > 25 ml/kg during the previous 24 h and the administration of high-dose vasopressors (0.2 μg · kg$^{-1}$ · min$^{-1}$ norepinephrine, or the equivalent dose of another vasopressor). | Synthetic human angiotensin II *vs.* placebo. | MAP response at 3 h after the start of infusion, defined as a MAP ≥ 75 mmHg or an increase in MAP from baseline ≥ 10 mmHg, without an increase in the dose of background vasopressors. | 114 of 163 patients (69.9%) in the angiotensin II group and 37 of 158 patients (23.4%) in the placebo group reached the primary endpoint (odds ratio, 7.95; 95% CI, 4.76 to 13.3; $P < 0.001$).<br>At 48 h, the mean improvement in the cardiovascular SOFA score was greater in the angiotensin II group than in the placebo group (–1.75 *vs.* –1.28; $P = 0.01$).<br>There were no significant differences (at $P < 0.05$) between the groups in the percentage of patients with adverse events. | Angiotensin II successfully increased blood pressure in patients with vasodilatory shock unresponsive to high doses of catecholamine vasopressors. |

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|---|---|---|---|---|---|---|
| Resuscitation targets—mean arterial pressure | | | | | | |
| SEPSISPAM; Asfar, 2014[18] | 776 patients with septic shock in 29 hospitals in France. | Adult patients with septic shock; refractory to fluid resuscitation; requiring vasopressors (norepinephrine or epinephrine) ≥ 0.1 μg · kg$^{-1}$ · min$^{-1}$; within 6 h after the initiation of vasopressors. Septic shock was defined as the presence of two or more diagnostic criteria of the systemic inflammatory response syndrome, proven or suspected infection, and sudden dysfunction of at least one organ. | High MAP target group (80 to 85 mmHg) *vs.* low MAP target group (65 to 70 mmHg). | Death from any cause by 28 days after enrollment. | 142 of 388 patients died in the high-target group (36.6%) and 132 of 388 in the low-target group had died at 28 days (34.0%; hazard ratio, 1.07; 95% CI, 0.84 to 1.38; $P = 0.57$). 170 patients (43.8%) and 164 (42.3%) had died at 90 days, respectively (hazard ratio, 1.04; 95% CI, 0.83 to 1.30; $P = 0.74$). Newly diagnosed atrial fibrillation events were reported in 26 patients (6.7%) in the high-target group and 11 patients (2.8%) in the low-target group ($P = 0.02$). Among patients with chronic hypertension, 53 of 167 patients (31.7%) in the high-target group required renal replacement therapy *vs.* 73 of 173 (42.2%) in the low-target group ($P = 0.046$). | Aiming for a mean arterial pressure of 80 to 85 mmHg during resuscitation of patients with septic shock, as opposed to a target range of 65 to 70 mmHg, did not yield significant differences in mortality. |
| 65 TRIAL; Lamontagne, 2020[19] | 2,463 older patients with vasodilatory hypotension in 65 ICUs in the United Kingdom. | Patients ≥ 65 yr of age; with vasodilatory hypotension; within 6 h of a vasopressor infusion initiation; with adequate fluid resuscitation (as assessed by the treating clinician); expected to continue vasopressor administration ≥ 6 h. Vasodilatory hypotension was defined as assessed by the treating clinician. | Permissive hypotension (MAP target, 60 to 65 mmHg) *vs.* usual care. | Death from any cause by 90 days after randomization. | 500 of 1,221 patients (41.0%) in the permissive hypotension and 544 of 1,242 (43.8%) in the usual care group had died in the hospital (absolute risk difference, –2.85%; 95% CI, –6.75 to 1.05; $P = 0.15$). Patients in the permissive hypotension group had lower exposure to vasopressors compared with the usual care group (difference in median duration, –5.0 h; 95% CI, –7.8 to –2.2 h; difference in median dose in norepinephrine equivalents, –8.7 mg; 95% CI, –12.8 to –4.6 mg). Subgroup of patients with septic shock: 262 of 589 patients (44.5%) in the permissive hypotension and 544 of 1,242 (43.8%) in the usual care group had died at 90 days (absolute risk difference, –2.85%; 95% CI, –6.75 to 1.05; $P = 0.15$). | Among patients 65 yr or older receiving vasopressors for vasodilatory hypotension, permissive hypotension compared with usual care did not result in a statistically significant reduction in mortality. |
| Resuscitation targets—arterial lactate | | | | | | |
| Jansen, 2010[20] | 348 patients with high lactate in 4 ICUs in the Netherlands. | Adult patients with blood lactate level ≥ 3.0 mEq/l on ICU admission. Excluded patients with liver failure. | Hemodynamic support targeting a decrease in the lactate level ≥ 20% every 2 h *vs.* usual care. | In-hospital mortality. | In the lactate group 58 of 171 patients (33.9%; $P = 0.067$) and in the control group 77 patients of 177 (43.5%) had died in the hospital (hazard ratio, 0.61; 95% CI, 0.43 to 0.87). Patients in the lactate were discharged earlier from the ICU (hazard ratio, 0.65; 95% CI, 0.50 to 0.85) and were weaned faster from mechanical ventilation (hazard ratio, 0.72; 95% CI, 0.54 to 0.98) and from inotropes (hazard ratio, 0.65; 95% CI, 0.42 to 1.00). | Among individuals admitted to the ICU with hyperlactatemia, the implementation of lactate-guided therapy resulted in a significant decrease in hospital mortality. |

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**Table 1.** (Continued)

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| Resuscitation targets—capillary refill time | | | | | | |
| ANDROMEDA-SHOCK; Hernández, 2019[21] | 424 patients with septic shock in 28 ICUs in five countries in Latin America. | Adult patients with septic shock, defined as suspected or confirmed infection, arterial lactate ≥ 2.0 mM and need of vasopressors to maintain a MAP ≥ 65 mmHg after an IV fluid load of ≥ 20 ml/kg greater than 60 min. | Resuscitation targeting normalization peripheral perfusion (capillary refill time) *vs.* resuscitation targeting normalization or decrease lactate by 20% every 2 h. | All-cause mortality at 28 days. | 74 patients (34.9%) in the peripheral perfusion group and 92 (43.4%) in the lactate group had died at 28 days (hazard ratio, 0.75; 95% CI, 0.55 to 1.02; $P = 0.06$).<br>In the peripheral perfusion group, there was significantly less organ dysfunction at 72 h after randomization (mean difference in SOFA score, −1.00; 95% CI, −1.97 to −0.02; $P = 0.045$), and patients received less resuscitation fluids within the first 8 h (mean difference, −408 ml; 95% CI, −705 to −110; $P = 0.01$). | In patients with septic shock, adopting a resuscitation approach aimed at restoring peripheral perfusion, as opposed to a strategy targeting serum lactate levels, did not lead to a reduction in 28-day mortality. |
| Resuscitation targets—central venous oxygen saturation | | | | | | |
| Rivers, 2001[22] | 263 patients with severe sepsis and septic shock in the emergency department of a single academic center in the United States. | Adult patients fulfilling two or more criteria for the systemic inflammatory response syndrome and with a systolic blood pressure < 90 mmHg (after a crystalloid-fluid challenge of 20 to 30 ml/kg over a 30-min period) or a serum lactate concentration ≥ 4 mM. | Early goal-directed therapy *vs.* usual care. | In-hospital mortality. | 38 of 130 patients (30.5%) in the early goal-directed therapy group and 59 of 133 (46.5%) in the usual care group had died in the hospital (relative risk, 0.58; 95% CI, 0.38 to 0.87; $P = 0.009$).<br>At 72 h, patients in the early goal-directed group had higher mean central venous oxygen saturation compared to usual care (70.4 ± 10.7% *vs.* 65.3 ± 11.4%; $P < 0.001$) and lower lactate concentrations (3.0 ± 4.4 *vs.* 3.9 ± 4.4 mM; $P = 0.02$). | The implementation of early goal-directed therapy in the emergency department yielded significant benefits in patients with severe sepsis and septic shock. |
| ProCESS; Yealy, 2014[23] | 1,341 patients with septic shock in 31 emergency departments in the United States. | Adult patients with two or more criteria for the systemic inflammatory response syndrome and a serum lactate level ≥ 4 mM or refractory hypotension, defined as systolic blood pressure that either was < 90 mmHg or required vasopressor therapy to maintain 90 mmHg after an IV fluid challenge. | Early goal-directed therapy *vs.* protocol-based standard-therapy *vs.* usual care. | 60-day in-hospital mortality. | 92 patients in the early goal-directed therapy group (21.0%), 81 in the protocol-based standard-therapy group (18.2%), and 86 in the usual-care group (18.9%) had died in the hospital at 60 days ($P = 0.83$).<br>The 60-day in-hospital mortality for the combined protocol-based groups did not differ significantly from that in the usual-care group (relative risk, 1.04; 95% CI, 0.82 to 1.31; $P = 0.83$), nor did when the groups were compared separately ($P$ ranging from 0.31 to 0.89). | Following a protocol-based resuscitation for patients diagnosed with septic shock in the emergency department did not result in improved outcomes. |
| ARISE; Peake, 2014[24] | 1,600 patients with septic shock in 51 emergency departments in Australia and New Zealand. | Adult patients with two or more criteria for the systemic inflammatory response syndrome and refractory hypotension (systolic blood pressure < 90 mmHg or MAP < 65 mmHg despite an IV fluid resuscitation of 1,000 ml in 60 min) or hypoperfusion (serum lactate level ≥ 4 mM). | Early goal-directed therapy *vs.* usual care. | All-cause mortality at 90 days. | 147 of 792 patients (18.6%) in the early goal-directed therapy group and 150 of 796 patients (18.8%) in the usual-care group had died at 90 days ($P = 0.90$). The absolute difference in the risk of death for the intervention group was − 0.3% (95% CI, −4.1 to 3.6). | Among critically ill patients arriving at the emergency department with early septic shock, the implementation of early goal-directed therapy did not lead to a reduction in all-cause mortality at 90 days. |

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**Table 1.** (Continued)

| Publication | Population and Setting | Main Inclusion Criteria | Comparison | Primary Outcome | Main Results | Conclusions |
|---|---|---|---|---|---|---|
| ProMISe; Mouncey, 2015[25] | 1,260 patients with septic shock in 56 emergency departments in England. | Adult patients with two or more criteria for the systemic inflammatory response syndrome and refractory hypotension (systolic blood pressure < 90 mmHg or MAP < 65 mmHg despite an IV fluid resuscitation of 1,000 ml in 60 min) or hyperlactatemia (serum lactate level ≥ 4 mM). | Early goal-directed therapy *vs.* usual care. | All-cause mortality at 90 days. | 90-day mortality: 184 of 623 patients (29.5%) in the early goal-directed therapy group *vs.* 181 of 620 patients (29.2%) in the usual care group had died at 90 days (relative risk. 1.01; 95% CI, 0.85 to 1.20; $P = 0.90$). | In patients experiencing early septic shock who received IV antibiotics and adequate fluid resuscitation adherence to an early goal-directed protocol for hemodynamic management did not result in improved outcomes. |

65 TRIAL, Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients with Vasodilatory Hypotension; AKI, acute kidney injury; ALBIOS, Albumin Italian Outcome Sepsis; ANDROMEDA-SHOCK, Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status *versus* Serum Lactate Levels on 28-Day Mortality among Patients with Septic Shock; ARISE, Australasian Resuscitation in Sepsis Evaluation; ATHOS-3, Angiotensin II for the Treatment of High-Output Shock; CENSER, Early Use of Norepinephrine in Septic Shock Resuscitation; CLASSIC, Conservative *versus* Liberal Approach to Fluid Therapy in Septic Shock; CLOVERS, Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis; HR, heart rate; ICU, intensive care unit; IV, intravenous; MAP, mean arterial pressure; ProCESS, Protocolized Care for Early Septic Shock; SAFE, Saline *versus* Albumin Fluid Evaluation; ProMISe, Protocolised Management in Sepsis; SEPSISPAM, Sepsis and Mean Arterial Pressure; SMART, Isotonic Solutions and Major Adverse Renal Events Trial; SOAP II, Sepsis Occurrence in Acutely Ill Patients II; SOFA, Sequential Organ Failure Assessment; SWIPE, Small volume resuscitation With 20% albumin in Intensive care: Physiologic Effects; VANISH, Vasopressin *versus* Norepinephrine as Initial Therapy in Septic Shock.

–4 beats/min) after fluid administration were not maintained at 1 and 2 h.[31]

Of note, testing fluid responsiveness ideally requires continuous cardiac output monitoring, which is not available in many settings.

The arterial waveform from invasive blood pressure monitoring can provide important insights into the hemodynamic profile. Low pulse pressure (*i.e.*, difference between systolic and diastolic pressure) may be a marker of low stroke volume,[32] indicative of low venous return (*i.e.*, hypovolemia), or cardiac dysfunction (left or right) or reduced ventricular filling time (*e.g.*, arrhythmias with rapid ventricular response). Changes in arterial pulse pressure, however, underestimate changes in stroke volume, and pulse pressure cannot replace actual measure of stroke volume of cardiac output.[32]

Low diastolic blood pressure likely indicates a low systemic vascular resistance and should favor using vasopressors over fluids. A differential diagnostic is severe aortic regurgitation. Of note, diastolic blood pressure is also impacted by the duration of the cardiac cycle. A higher HR increases diastolic pressure.

Finally, indicators of poor fluid tolerance (*e.g.*, signs of venous congestion, elevated cardiac filling pressure) may identify patients who are more likely to suffer the harmful effects of fluid administration (fig. 1) or, in the most severe cases, even benefit from fluid removal after the initial phase of resuscitation (*i.e.*, 24 to 48 h). Elevated central venous pressure (CVP; greater than 12 to 15 mmHg in mechanically ventilated patients), elevated brain natriuretic peptides, or altered venous Doppler should prompt consideration of organ venous congestion. The venous excess ultrasound score, encompassing assessments of hepatic venous, intrarenal venous Doppler, and inferior vena cava to portal vein Doppler, assesses organ perfusion and elevated organ venous pressures.[33] Currently, its use patients with septic shock in is being explored through a multicenter prospective cohort study.[34]

*Fluid Resuscitation in Practice.* "Low-volume" initial fluid resuscitation (1 to 3 l) is safe and limits potential harm of excess fluid administration during the early resuscitation of sepsis. Patients with persistent hypoperfusion (*e.g.*, mottled skin, increased capillary refill time, low central venous oxygen saturation, low urine output) or requiring rising doses of vasopressors should be explored for fluid responsiveness or cardiac dysfunction. Limiting fluid maintenance is advised in most patients. Finally, signs of venous congestion should prompt clinicians to stop fluid administration and to consider fluid removal (most often after the initial phase).

## Which Fluid?

Normal saline has been associated with a higher risk of hyperchloremic metabolic acidosis.[35] When compared to balanced solutions such as lactated Ringer's solution or Plasmalyte, normal saline may have an adverse effect on kidney function and survival. In the Isotonic Solutions and Major Adverse Renal Events Trial (SMART), 15,802 adults were randomized to saline or balanced crystalloids. The balanced group had 14.3% major kidney events *versus* 15.4% in the saline group.[9] In a secondary analysis of the 1,641 septic patients, the balanced crystalloids group showed a lower 30-day in-hospital mortality compared to the saline group.[9] A Bayesian meta-analysis of 13 randomized controlled trials, comprising 35,884 critically ill participants, demonstrated a high probability of a beneficial average

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**Table 2.** Fluid Responsiveness Assessment

| Dynamic Test | Physiologic Basis | Execution | Response | Performance | Advantages | Limitations |
|---|---|---|---|---|---|---|
| Passive leg raising[2629] | Passive leg raising induces a translocation of venous blood from the legs to the intrathoracic compartment, resulting in a transient increase in cardiac preload. It has an effect comparable to a 300-ml rapid fluid infusion. | Changing a patient's bed position from semirecumbent to horizontal, with lower limbs elevated at a 45-degree angle without touching the patient. | Pulse pressure or stroke volume elevation > 10–15%, within 1 min of a passive leg raising test, identifies patients who are more likely to increase cardiac output in response to a fluid bolus. | Pooled sensitivity, 77% (95% CI, 73–80%); pooled specificity, 80% (95% CI, 75–83%). | Does not require fluid administration.<br>Results are independent from breathing effort, cardiac rhythm, tidal volume, or lung compliance. | Requires invasive arterial pressure monitoring or stroke volume monitoring to assess the response.<br>Risk of false negative:<br>-Augmented intra-abdominal pressure.<br>-Compressive antithrombotic prophylaxis. |
| End-expiratory occlusion test[27,29] | Heart–lung interactions:<br>- During a positive pressure mechanical ventilation cycle, the stroke volume varies because of cardiopulmonary interactions.<br>- During insufflation, the intrathoracic pressure increases, leading to a reduction in venous return. Subsequently, the right ventricle stroke volume is minimized.<br>- This causes a decrease in left ventricular venous return and preload after the blood transition through the pulmonary circulation.<br>- In fluid-responsive subjects, the reduction in left ventricle preload leads to a decrease in left ventricle stroke volume. | Interruption of mechanical ventilation at the end of expiration for at least 12 s, while maintaining positive end-expiratory pressure level. | In fluid-responsive subjects, the occlusion of the ventilatory interface halts the cyclical reduction in stroke volume induced by positive pressure ventilation.<br>A pulse pressure variation > 3.5–5% after an end-expiratory occlusion test identifies patients who are more likely to increase cardiac output in response to a fluid bolus. | Pooled sensitivity, 76% (95% CI, 70–81%); pooled specificity, 77% (95% CI, 71–83%). | Simple execution.<br>Results are independent of breathing effort, cardiac rhythm, tidal volume, and lung compliance. | Requires mechanical ventilation.<br>Spontaneously breathing patients may be unable to endure the occlusion test.<br>Risk of false negative in acute respiratory distress syndrome (low tidal volume or low lung compliance). |
| Pulse pressure variation[29] | Heart–lung interactions, as described above | Real-time measurement of the difference between systolic pressure and diastolic pressure during mechanical ventilation. | The pulse pressure variation reflects the cyclic respiratory changes in stroke volume.<br>A pulse pressure variation > 12–15% between inspiration and expiration identifies patients who are more likely to increase cardiac output in response to a fluid bolus. | Pooled sensitivity, 77% (95% CI, 74–80%); pooled specificity, 79% (95% CI, 76–82%). | Automatic assessment.<br>No requirement of cardiac output assessment. | Requires mechanical ventilation.<br>Requires invasive arterial pressure monitoring.<br>Risk of false positive:<br>-Spontaneous breathing.<br>-Cardiac arrhythmia.<br>-Augmented intra-abdominal pressure.<br>-Right heart failure.<br>Risk of false negative:<br>-Heart rate to respiratory rate ratio < 3.6.<br>-Open chest.<br>-Acute respiratory distress syndrome (low tidal volume or low lung compliance). |

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**Table 2.** (Continued)

| Dynamic Test | Physiologic Basis | Execution | Response | Performance | Advantages | Limitations |
|---|---|---|---|---|---|---|
| Stroke volume variation[29] | Heart–lung interactions, as described above | Real-time pulse contour analysis of the profile of the arterial pressure profile *via* a dedicated device. | A stroke volume variation > 12–15% between inspiration and expiration identifies patients who are more likely to increase cardiac output in response to a fluid bolus. | Pooled sensitivity, 77% (95% CI, 73–80%); pooled specificity, 78% (95% CI, 74–82%). | Automatic assessment. | Requires mechanical ventilation.<br>Requires invasive arterial pressure monitoring and pulse contour analysis.<br>Risk of false positive:<br>-Spontaneous breathing.<br>-Cardiac arrhythmia.<br>-Augmented intra-abdominal pressure.<br>-Right heart failure.<br>Risk of false negative:<br>-Heart rate to respiratory rate ratio < 3.6.<br>-Open chest.<br>-Acute respiratory distress syndrome (low tidal volume or low lung compliance). |
| Tidal volume challenge[29] | Heart–lung interactions, as described above | Transient (1 min) increase of tidal volume from 6 ml/kg of predicted body weight to 8 ml/kg of predicted body weight. | A change in pulse pressure variation and stroke volume variation > 2–3.5% after a tidal volume challenge identifies patients who are more likely to increase cardiac output in response to a fluid bolus. | Pooled sensitivity, 86% (95% CI, 81–91%); pooled specificity, 80% (95% CI, 74–85%). | This test overcomes pulse pression variation unreliability with low tidal volume ventilation.<br>Results are independent from breathing effort and prone positioning. | Requires mechanical ventilation.<br>Risk of false positive:<br>-Cardiac arrhythmia.<br>-Augmented intra-abdominal pressure.<br>Limited validation studies and variability between cutoffs adopted |
| Mini-fluid challenge[28,29] | Additional fluid infusion increases the volume of venous return to the heart. In fluid responder patents, this increase in preload leads to an increase in stroke volume, according to the Frank–Starling principle. | Rapid infusion of 100 ml fluids over 1 min. | An increase > 10–12% in velocity time index (transthoracic echocardiography) or stroke volume identifies patients who are more likely to increase cardiac output in response to a fluid bolus. | Pooled sensitivity, 85% (95% CI, 79–90%); pooled specificity, 84% (95% CI, 78–88%). | Simple and pragmatic execution.<br>Results are independent from breathing effort, cardiac rhythm, tidal volume, lung compliance, or intra-abdominal pressure. | Requires real-time stroke volume monitoring to assess the response.<br>Requires administration of fluids that cannot subsequently be withdrawn. |

Dynamic tests predict whether stroke volume will increase after fluid administration.

effect of balanced solution on mortality.[36] In a subset of 6,754 patients with sepsis, the use of balanced crystalloids, when compared to saline, was associated with a reduction in mortality risk of 0.93, although not statistically significant (95% CI, 0.86 to 1.01; $I^2$ = 22.3%).[36] Of note, balanced solutions (especially lactated Ringer's solution) are hypoosmotic and should not be used in patients with brain injury.[37] The 2021 surviving sepsis guidelines suggest using balanced crystalloids instead of normal saline for resuscitation in patients with sepsis, with a weak recommendation (of note, guidelines were issued before the publication of the abovementioned meta-analysis). Finally, ionized calcium should be monitored when administering Plasmalyte given the risk of hypocalcemia.

The role of albumin in sepsis has long been debated. In the Saline versus Albumin Fluid Evaluation (SAFE) trial, the use of hypo-oncotic (4%) albumin *versus* normal saline resulted in similar 28-day outcomes.[10] In a subgroup of 1,218 patients with severe sepsis, 28-day mortality was 30.7% in those assigned to receive albumin *versus* 35.3% in those in the normal saline group, a difference that suggests possible benefit for albumin use in sepsis.[10] In the multicenter Albumin Italian Outcome Sepsis (ALBIOS) trial, 1,818 patients with severe sepsis were randomized to receive either 20% albumin or crystalloids with a target serum albumin concentration 30 g/l or greater, and found no significant difference in 28-day mortality.[11] The albumin group had a significantly higher MAP and lower net fluid balance during the first 7 days of study.[11] Patients with septic shock who received albumin had a lower risk of 90-day mortality.[11]

In the Small volume resuscitation With 20% albumin in Intensive care: Physiologic Effects (SWIPE) trial, 321

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critically ill patients received 20% *versus* 4 to 5% albumin. The 48-h fluid balance was lower with 20% albumin (−600 ml), and the proportion discharged alive from the intensive care unit was 97.4% *versus* 91.1%, but in a sensitive analysis for sepsis, differences were not significant[12] (table 1).

*Type of Fluid in Practice.* Taken together, current evidence suggests that balanced crystalloid solutions should be the first-line fluid for sepsis resuscitation unless specific contraindications exist such as hyponatremia or brain injury. Albumin (especially hyper-oncotic) may decrease fluid balance, but its impact on outcomes remains uncertain in septic shock and is likely minimal if exists. The higher cost of albumin should also be taken into account. The ongoing Albumin Replacement Therapy in Septic Shock (ARISS) trial (NCT 03869385) will provide more information about the impact of albumin on mortality in septic shock.

## Early Vasopressors Administration

Strategies of early vasopressor administration have been suggested to reduce fluid balance and improve outcomes. Norepinephrine can increase systemic venous return through venous vasoconstriction and increased stressed volume,[38] and decrease endothelial permeability and fluid loss into the extravascular space.[39]

Recent data suggest that early peripheral vasopressor administration is remarkably free of adverse effects.[40] A meta-analysis of 16,055 patients reported a low incidence (1.8%) of local adverse events directly associated with vasopressor infusion in a peripheral vein.[40] In particular, clinicians should not wait until central access is obtained before initiating vasopressor treatment. Vasopressor administration can be considered as early as severe hypotension is confirmed, even if the patient is still fluid responder.[38]

In a propensity score–matched study, vasopressor administration within the first hour of resuscitation was associated with significantly lower 24-h fluid balance (3,905 *vs.* 5,400 ml) and 28-day mortality compared to those who started vasopressors after 1 h (hazard ratio, 0.31).[41] In a single-center trial including 310 patients, early norepinephrine administration significantly improved shock control (defined as achieving target MAP and perfusion) at 6 h when compared to standard treatment (76.1% *vs.* 48.4%) and was associated with reduced pulmonary edema (14.4% *vs.* 27.7%) and arrhythmic events (11% *vs.* 20%).[13]

In the CLOVERS trial, vasopressors use was more frequent (21.7%) and started earlier (−1.4 h) in the restrictive group, although the outcome was not different.[14]

Finally, in patients with septic shock, hydrocortisone is associated with more vasopressor-free days, and the evidence suggests a benefit on mortality with an early and short (5 to 7 days) course of hydrocortisone (200 mg/day) plus fludrocortisone (50 μg/day).[42]

## Which Vasopressor?

Norepinephrine, a predominant α-1 and β-1-adrenergic agonist, is the first-line vasopressor recommended for septic shock and has been linked to reduced adverse effects compared to dopamine.[2,15] No other vasopressor has shown improved outcomes compared to norepinephrine so far, and a shortage of norepinephrine in the United States was associated with increased mortality.[43] However, norepinephrine can contribute to the downregulation of adrenergic receptors in the cardiovascular system and nonhemodynamic effects such as immune dysregulation.[44]

Low doses of vasopressin, a V1 receptor agonist, can be considered in addition to norepinephrine in selected patients (low quality of evidence).[2] Vasopressin use has been associated with a reduction of catecholamine requirements and a lower risk of atrial fibrillation (risk ratio, 0.77; 95% CI, 0.67 to 0.88).[45] High doses (above 0.04 U/min) may, however, lead to coronary, mesenteric, or digital ischemia.[16] Furthermore, excessive vasoconstriction can impair cardiac function.[46] Initiating vasopressin early (when norepinephrine is less than 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) may therefore limit exposure to catecholamines in patients with hyperkinetic septic shock and rapid rising doses of norepinephrine. However, vasopressin in patients with severely altered left ventricular function or with poor peripheral perfusion (*i.e.*, elevated capillary refill time) may further alter cardiac output. Assessment of cardiac function in patients receiving vasopressin is advised. In isolated radial and pulmonary arterial segments, vasopressin differed from other vasoconstrictors as causing only radial and not pulmonary vasoconstriction.[47] These data suggest that vasopressin may limit the increase of right ventricle afterload in patients with compromised right ventricular function and pulmonary hypertension.

Angiotensin II use as a second-line blood vasopressor successfully raised blood pressure in patients with refractory vasodilatory shock.[17] In these patients, an increase in the angiotensin I/angiotensin II ratio has been associated with poor outcomes, suggesting a defect in circulating angiotensin II levels. Similarly, a defect in angiotensin II signaling with decreased angiotensin II receptor 1 expression has been reported in sepsis-associated AKI.[48] *Post hoc* studies of the Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) trial[17] have suggested a beneficial effect on mortality in patients with high renin levels at baseline and patients requiring renal replacement therapy at angiotensin II initiation.[49] Therefore, angiotensin II may be considered in these selected patients with severe sepsis-associated AKI or high renin levels (which is most of the time not readily available). However, further clinical studies are needed to confirm these beneficial effects, as adverse events have been identified, especially related to thromboembolic events, venous and arterial, and fungal infections. Given the increased risk of thromboembolic events, special attention must be given to thromboembolic prevention in case of angiotensin II use.

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*Vasopressors in Practice.* Early vasopressor use appears safe, reducing time to hypotension correction and fluid balance. Norepinephrine is the first-line vasopressor therapy. Second-line vasopressors may be considered for patients with specific comorbidities: vasopressin in cases of high risk of atrial fibrillation and patients with hyperkinetic septic shock with elevated cardiac output. Angiotensin II is promising for patients with severe AKI, but further studies are needed.

### Assessment of Cardiac Function and Inotropes

Sepsis is associated with sepsis-induced cardiomyopathy in up to 50% of cases, and a new-onset left ventricle dysfunction, with ejection fraction less than 50%, is associated with increased in-hospital mortality.[50] Focused critical care echocardiography in patients with hemodynamic instability can explore (1) left-ventricular cardiac dysfunction, (2) right-ventricular cardiac dysfunctions or right-ventricular dilation, and (3) evidence of severe hypovolemia (*i.e.*, kissing left ventricle with collapsible inferior vena cava), or (4) rule out tamponade. Although rare, inquiring about severe valvopathy (*e.g.*, severe aortic regurgitation or mitral regurgitation) would have important therapeutic implications in patients with shock or pulmonary edema.

Although patients with sepsis often have a hyperdynamic circulation, inotropes may be considered in patients with severe left- or right-ventricular dysfunction persistent shock, and hypoperfusion, mostly dobutamine and levosimendan.[51] Dobutamine acts predominantly as a β-1-adrenergic receptor agonist, while levosimendan improves cardiac contractility *via* a calcium-sensitizing mechanism. A meta-analysis of six randomized controlled trials, including 192 patients with sepsis-induced cardiac dysfunction, found no difference between levosimendan and dobutamine on mortality.[52] Treatment with levosimendan was associated with a greater improvement of cardiac index and a significant decrease of blood lactate at 24 h when compared with dobutamine.[52]

Epinephrine enhances contractility *via* β-1 receptors and causes vasoconstriction *via* α-1 receptors. In a meta-analysis of 12 randomized controlled trials (52.5% patients with septic shock), epinephrine use was linked to a trend of elevated HR and blood lactate levels, potentially complicating perfusion assessment, without a benefit in mortality and concerns of decreased gut perfusion.[53]

In patients with right ventricular dysfunction or dilation, strategies to limit right ventricular afterload (*e.g.*, decrease positive end-expiratory pressure, inhaled nitric oxide) and inotropes can improve right ventricular function, limit venous congestion, and improve perfusion.

*Inotropes in Practice.* If available, bedside cardiac ultrasound or focused critical care echocardiography provide more information in patients with hemodynamic instability and help to rule out cardiac dysfunction.[54] In patients with severe left or right ventricular dysfunction, persistent shock, and hypoperfusion, inotropes (*e.g.*, dobutamine, levosimendan) should be considered. Depending on the setting and expertise, hemodynamic monitoring using a pulmonary artery catheter and or methods like transthoracic thermodilution can allow assessment of hemodynamic profiles.

## Resuscitation Targets

### Mean Arterial Pressure

The Sepsis and Mean Arterial Pressure (SEPSISPAM) trial compared low-MAP (65 mmHg) to high-MAP (85 mmHg) targets in septic shock and found no significant differences in 28-day mortality (hazard ratio in the high-target group, 1.07) or 90-day mortality (hazard ratio, 1.04).[18] In a subpopulation of patients with chronic hypertension, fewer patients in the high-target group (31.7%) required renal replacement therapy than in the low-target group (42.2%), but the criteria for renal replacement therapy were not protocolized.

Conversely, in a trial involving 2,463 patients at least 65 yr old with hypotension, vasopressors guided by a permissive MAP target (60 to 65 mmHg) resulted in significantly lower vasopressor exposure (–8.7 mg norepinephrine equivalent dose), but not a significant difference in 90-day mortality in the subgroup analysis for sepsis or septic shock.[19]

Altogether, there is no evidence that targeting MAP above 65 mmHg could improve outcomes. Targeting higher MAP would require higher doses of vasopressors. This has been associated with a higher incidence of atrial fibrillation[18] and a trend toward higher mortality.[19] However, individualized targets might be appropriate in specific situations after a "vasopressor trial" testing the impact and tolerance of higher blood pressure targets (long-standing poorly controlled hypertension, patients with critical arterial stenosis, and others).

Elevated CVP has been repeatedly associated with an increased risk of organ failure, especially AKI, and rising CVP (greater than 12 mmHg) should alert clinicians to the risk of venous congestion and trigger actionable measures (*e.g.*, fluid removal, improve cardiac function).[55]

### Arterial Lactate

Hyperlactatemia underlying mechanisms during sepsis may include anaerobic glycolysis in poorly perfused areas, the metabolic effect of adrenergic stimulation, reduced hepatic clearance, and mitochondrial dysfunction. In a *post hoc* analysis of the ALBIOS trial,[11] 90-days mortality was significantly and progressively increased across higher sextiles of lactate levels ($P < 0.001$).[56] Hyperlactatemia was reported to be more frequently associated with impaired tissue oxygen use, rather than by impaired oxygen transport.[56] A strategy targeting a reduction of at least 20% in lactate levels every 2 h during the first 8 h was tested in a trial of 348 patients, with the control group only informed

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of the admission value.[20] The lactate group demonstrated significantly lower in-hospital mortality (hazard ratio, 0.61), significantly higher volumes of fluids at 8 h of resuscitation (2,697 *vs.* 2,194 ml), and reduced Sequential Organ Failure Assessment scores observed at 72 h (6.4 *vs.* 7.0).[20]

## Capillary Refill Time and Mottled Skin

Capillary refill time is an easy and widely accessible way to assess peripheral perfusion, measuring the time taken for the skin to return to its normal color after pressure is applied to a distal capillary bed. A prolonged time (greater than 3 s) is significantly associated with increased mortality (odds ratio, 1.3).[57] Increased capillary time and mottled skin correlate well with alteration of the microcirculation identified with more advanced tools.[58]

The Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status *versus* Serum Lactate Levels on 28-Day Mortality among Patients with Septic Shock (ANDROMEDA-SHOCK) trial randomized 424 patients with septic shock to an approach guided by capillary refill time normalization (assessed every 30 min) or by 20% or greater decrease in lactate levels per 2 h during an 8-h study period.[21] After initial resuscitation to maintain a MAP 65 mmHg or greater, both groups were managed using a standardized protocol. Fluid responsiveness assessment was integrated as the first step, 500 ml of crystalloids were administered to fluid responders until the goal was achieved or a CVP limit was reached, or if the patient became fluid-unresponsive. The protocol included the use of a vasopressor test for patients with previous chronic hypertension and an inodilator test for patients who were nonresponders to vasopressors. The 28-day mortality was not significantly different between the peripheral perfusion group (34.9%) and the lactate group (43.4%; hazard ratio, 0.75).[21] Nonetheless, the intervention group received less fluid in the first 8 h of resuscitation (−408 ml) and presented a lower incidence of organ dysfunction at 72 h (mean difference in Sequential Organ Failure Assessment score, −1.00) when compared to the lactate group.[21] A Bayesian reanalysis suggested that the peripheral perfusion strategy was significantly associated with lower odds of mortality at both 28 days (odds ratio, 0.61) and 90 days (odds ratio, 0.68).[59] The ANDROMEDA-SHOCK-2 trial will assess the effect of a capillary refill time–targeted strategy based on hemodynamic phenotyping of septic shock patients (NCT 05057611).

Skin mottling results from heterogeneous vasoconstriction in small blood vessels and is believed to reflect aberrant microcirculation. The mottling score is a reproducible indicator that quantifies the irregular skin discoloration that initiates at the knees, on a scale of 0 to 5, with higher values indicating a greater extension. High scores (4 to 5) are strong predictors of 14-day mortality in patients with septic shock (odds ratio, 74; 95% CI, 11 to 1,568).[60] This measure has been integrated into recent randomized trial protocols addressing resuscitation in sepsis.[7,14]

## Central Venous Oxygen Saturation

Central venous oxygen saturation reflects the balance between oxygen delivery and consumption (fig. 1). Low values can indicate inadequate oxygen delivery due to low cardiac output, low hemoglobin level, and/or low arterial oxygen saturation and are associated with higher mortality rates.[56] However, high values do not rule out hypoperfusion given the potential decrease of oxygen consumption in sepsis.

In a monocentric study, the implementation of early goal-directed therapy with central venous oxygen saturation optimization has been linked to significantly lower in-hospital mortality rates compared to a standard therapy group (30.5% *vs.* 46.5%), higher mean central venous oxygen saturation (70.4% *vs.* 65.3%), and lower lactate concentrations (3.0 *vs.* 3.9 mM).[22] However, subsequent multicenter randomized trials did not confirm these results.[23–25] A meta-analysis showed no significant difference in 90-day mortality between the early goal-directed therapy approach and usual care (24.9% and 25.4%).[61] This contrasting evidence might be attributed to changes in clinical practice over the years, the timing of the intervention, and differences in the severity of illness among populations in the latest trials[23–25] (table 1). Furthermore, the overall 28-day mortality rate was lower in the usual care group of these more recent trials (20.6%)[61] compared to the intervention group of the original early goal-directed study (33.3%).[22]

## Urine Output

Oliguria is associated with worse outcomes in sepsis[62] and has long been a main trigger for fluid boluses.[63] However, urine output is influenced by neurohormonal regulation and kidney injury (*e.g.*, acute tubular injury), and oliguria is a poor indicator of fluid responsiveness. In a multicenter prospective study, only 50% patients with oliguria for 3 consecutive hours were responders to a fluid challenge.[64] Urine sodium concentration and fractional excretion of sodium were not predictive of fluid responsiveness.[64]

In a secondary analysis of 127 patients from the Fluid and Catheter Treatment Trial,[65] no significant changes in urine output were observed after a fluid bolus in patients with low urine output.[66]

*Perfusion Targets in Practice.* A MAP target of 65 mmHg is appropriate in most patients. Nevertheless, individualized targets might be suitable in specific situations.

Hyperlactatemia and oliguria are not a specific biomarker of tissue (hypo)perfusion but are associated with increased mortality and should prompt a thorough hemodynamic evaluation. Likewise, while monitoring of central venous oxygen saturation in all patients is not advised, a low central venous oxygen saturation in patients with organ failure or signs of peripheral hypoperfusion should raise concerns for inappropriate oxygen delivery. Finally, capillary refill time and mottled skin are accessible and valid

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biomarkers of hypoperfusion and can help guide therapeutic interventions (fig. 1).

## Conclusions

Results of recent randomized trials have refined our understanding of the best management of sepsis and help guide treatment rules, especially favoring the use of balanced crystalloids solutions, exploring the safety of a more restrictive approach with fluid resuscitation, and emphasizing the role of peripheral perfusion assessment to guide resuscitation. Future research should explore the role of different hemodynamic targets and parameters to guide resuscitation, strategies targeting the microcirculation, and the impact of different vasopressors and fluid solutions such as albumin.

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## Competing Interests

Dr. Legrand received consulting fees from Alexion (Boston, Massachusetts) and La Jolla (Waltham, Massachusetts). The other authors declare no competing interests.

## Correspondence

Address correspondence to Dr. Legrand: Department of Anesthesia & Perioperative Care, Division of Critical Care Medicine, University of California, San Francisco, 521 Parnassus Avenue, San Francisco, California 94143. matthieu.legrand@ucsf.edu

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